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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,417	PAGANO, MICHELE	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-9 have been amended. Claims 10-21 have been added. Claims 1-21 are pending and under consideration.

2. Sections of Title 35, U.S. Code not found in this action can be found in a prior action.

3. Claims 7-12 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 9 recite "polypeptide corresponding to the carboxy terminus of the human p27 chain". The metes and bound of a peptide "corresponding to" a specific amino acid sequence is unclear because it is unknown if "corresponding to" and amino acid sequence includes a polypeptide "comprising" said amino acid sequence and likewise it is unclear if "corresponding to" an amino acid sequence allows for a partial degree of correspondence permitting some deviation in said amino acid sequence in terms of substitution, deletion or addition of a portion of said amino acid sequence.

4. Claims 1, 3, 4, 6-11, 18, 20 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) As drawn to molecules which interact with Skp2

The instant claims are drawn to methods reliant upon the description of a Skp2 binding activity and/or the description of Skp2 ubiquiting ligase activity. The specification describes a Skp2 ubiquiting ligase activity as being measured in binding to the target protein, p27, and that Cks1 is present in a complex with Skp2. However, the art recognizes that it is likely that skp2 targets substrates other than p27 for ubiquitination and speculates that candidates for said substrates could be E2F1, cyclin D1 and p21 (page 198, first column, lines 16-17 in the fourth paragraph in Carrano et al, Nature Cell Biology, Aug 1999, Vol. , pp. 193-199). Skp2 binding

activity is thus read as encompassing association with Skp2 in a complex as well as interaction with a target protein and Skp2. Thus, the disclosure of Skp2 associating with Cks1 and binding to p27 (page 7, line 34 to page 8, line 1) does not adequately describe the wider genus of Skp2-binding activity because p27 can be one of several different molecules targeted by Skp2 and there is no structural or functional nexus between p27 and any other purported targets of Skp2, such as the E2F1, cyclin D1 and p21 cited by Carrano et al.. One of skill in the art would reasonable conclude that applicant was not in possession of Skp2-binding activity beyond that of Skp2-p27 at the time of the invention.

(B) As drawn to polypeptide corresponding to SEQ ID NO:91

Claims 7-12 are method claims reliant upon the identity of a polypeptide corresponding to the carboxy terminus of the human p27 chain having the sequence of SEQ ID NO:91. When given the broadest reasonable interpretation polypeptides corresponding to SEQ ID NO:91 can be read as polypeptides which have a degree of correspondence to SEQ ID NO:91. Thus, claim 7 and 12 are reliant upon a genus of polypeptides which differ in structure from SEQ ID NO:91. The specification has not provided a representative number of examples which would serve to describe this genus, nor has the specification taught the correlation between the structure of SEQ ID NO:1 necessary for recognition and binding to Skp2 beyond that of being phosphorylated on tyrosine. Thus, the genus of polypeptides "corresponding to" SEQ ID NO:91 is variant and the disclosure of SEQ ID NO:91 fails to adequately represent this genus because the genus tolerates member which differ by an unknown degree and nature from that of SEQ ID NO:91. One of skill in the art would reasonable conclude that applicant was not in possession of the genus of polypeptides corresponding to SEQ ID NO:91.

Because the applicant was not in possession of the products on which the instant method claims require, it follows that applicant was not in possession of the instant method claims.

5. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carrano et al (Nature Cell Biology, 1999, Vol. 1, pp. 193-199) as evidenced by Ganoth et al (Nature Cell Biology, 2001, Vol. 3, pp. 321-324).

Claim 1 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorder comprising contacting a compound with a cell or cell

extract expressing Cks1 and Skp2, and detecting a change in Skp2-binding activity or Skp2-ubiquitin ligase activity. Claim 2 embodies the method of claim 1 wherein the change in Skp2 binding activity is detecting by detecting a change in the binding of Skp2 with either p27 or Csk1. Claim 3 embodies the method of claim1 wherein the change in Skp2- ubiquitin ligase activity is detected by detecting a change in the ubiquitination or degradation of a Skp2-specific substrate.

Claim 4 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising adding a compound to a mixture containing Cks1 and Skp2 and detecting a change in Skp2-binding activity or Skp2- ubiquitin ligase activity. Claim 5 embodies the method of claim 4 wherein the change in Skp2 binding activity is detected by detecting a change in binding of Skp2 with either p27 or Csk1. Claim 6 embodies the method of claim 4 wherein the change in the activity of Skp2- ubiquitin ligase activity is detected by detecting a change in the ubiquitination or degradation of a Skp2-specific substrate.

Claim 7 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising adding a compound to a mixture containing Skp2 and one or both of (i) a polypeptide corresponding to the carboxy terminus of the human p27 chain with or without a phosphothreonine at position 8 and (ii) Cks1; and detecting a change in the interaction of Skp2 with the polypeptide of Cks1. Claim 8 embodies the method of claim 7 wherein the change in the interaction of Skp2 with Csk1 or the polypeptide is detected by detecting a change in the binding of Skp2 to either Csk1 or the polypeptide.

Claim 10 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising adding a compound to a mixture containing Skp2 and one or both of (i) a polypeptide corresponding to the carboxy terminus of the human p27 chain with or without a phosphothreonine at position 8 and (ii) Cks1; and detecting a change in Skp2 ubiquiting ligase activity. Claim 11 embodies the method of claim 10 wherein the change in Skp2 ubiquitin ligase activity is detected by detecting a change in the ubiquitination or degradation of the polypeptide or a Skp2-specific substrate. Claim 12 embodies the method of claim 3, 6 or 11 wherein the Skp2-specific substrate is p27.

Claim 13 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising contacting a compound with a cell or a cell

extract expressing Cks1, p27 and Skp2 and detecting a change in Skp2 binding activity or Skp2 ubiquiting ligase activity. Claim 14 embodies the method of claim 13 wherein the change in Skp2-binding activity is detected by detecting a change in the binding of Skp2 with either p27 or Cks1. Claim 15 embodies the method of claim 13 wherein the change in the Skp2 ubiquiting ligase activity is detected by detecting a change in the ubiquitination or degradation of p27.

Claim 20 embodies the method of claim 1 or claim 13, wherein the cell or cell extract further expresses Cyclin E and Cdk2.

Claim 16 is drawn to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising adding a compound to a mixture comprising Cks1, p27 and Skp2 and detecting a change in Skp2 binding activity or Skp2 ubiquiting ligase activity. Claim 17 embodies the method of claim 16 wherein the change in Skp2-binding activity is detected by detecting a change in the binding of Skp2 with either p27 or Cks1. Claim 18 embodies the method of claim 16 wherein the change in the Skp2 ubiquiting ligase activity is detected by detecting a change in the ubiquitination or degradation of p27. Claim 19 embodies the method of claim 16 wherein the Skp2-specific substrate is p27.

Claim 21 embodies the methods of claim 4, 7, 10 or 16 wherein the system further contains Cyclin E and Cdk2.

Carrano et al teach that Skp2 is required for ubiquitin mediate degradation of p27. Carrano et al teach that the combined addition of Skp1-Skp2 and cyclinE-CDK2 to G1 extracts of HeLa cells markedly stimulated p27 proteolysis (page 195, first column, lines 16-23). Carrano et al teach that Skp2 and Cyclin E-cdk2 are rate limiting for p27 ubiquitination on G1 extracts (legend for Figure 3). Carrano et al teach that in many cancer cell lines, Spk2 levels are high and that a specific small-molecule inhibitor of Skp2 should increase the cellular abundance of p27 and lead to a block in cellular proliferation and disease progression (page 198, last paragraph).

The HeLa cell extracts used by Carrano et al comprise Cks1 as evidenced by Ganoth et al who teach that Cks1 is present in HeLa cell extracts (lines 9-12 of abstract, and lines 10-11 in the first paragraph under the abstract).

It would have been prima facie obvious at the time the claimed invention was made to screen for a specific small-molecule inhibitor of Skp2 which would increase the cellular

abundance of p27 by measurement of the interaction between Skp2 and p27 measured by Skp2-binding to p27 or the resulting proteolysis of ubiquitinated p27 by adding a candidate small molecule inhibitor to HeLa G1 extracts comprising adding Skp1-Skp2 and cyclinE-CDK2 to said extracts and contacting the mixture with a candidate inhibitor. One of skill in the art would be motivated to do by the suggestion of Carrano et al that a small molecule inhibitor of Skp2 would result in increased levels of p27 and concomitant decrease in cellular proliferation.
Carrano et al fulfill the specific limitation of the claims with regard to composition and Skp2 binding or ubiquitin ligase activity because the Cks1 is inherently present in the mixture. Carrano et al fulfill the specific limitation of claims 2, 5, 7, 8, 9, 10, 14, 17 with respect to the binding of Skp2 because Cks1 is listed in the alternative. Carrano et al fulfill the specific limitation of claim 7 and 9 with regard to a polypeptide corresponding to the carboxy terminus of the human p27 protein because one reasonable interpretation of "corresponding to" said protein is the full length p27 protein.

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

An obviousness-type double-patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. In reBerg, 140 F.3d, 1428, 46 USPQ2d 1226 (Fed. Cir. 1998): In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993): In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-22 of copending Application No. 10/632,150 in view of Carrano et al (Nature Cell Biology, 1999, Vol. 1, pp. 193-199).

The instant claims are obvious over the claims 20-22 of '150 in view of Carrano et al who teach that Skp2 is required for ubiquitin mediate degradation of p27. One of skill in the art would have been motivated to detect the "activity" of Skp2 by measured by ubiquitination or proteolysis of p27 which is taught by Carrano et al.

This is a provisional obviousness-type double patenting rejection.

8. Claims 1-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of copending Application No.s 11/073,457, 11/073,460, 11/073,470 and 11/073485. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '457, '460, '470 and '485 applications anticipate the instant claims .

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

9. All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
10/04/2005